Indications, Protocols, and Outcomes of Drug Desensitizations for Chemotherapy and Monoclonal Antibodies in Adults and Children

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Activity Objectives

1. To learn the process of evaluating patients with hypersensitivity reactions to chemotherapy and monoclonal antibodies (mAbs).

2. To become familiar with current protocols used for desensitization to chemotherapy and mAbs.

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Advances in the understanding of various malignancies and chronic inflammatory diseases has led to the development of better treatment options for prolonging patient survival and minimizing morbidity. The recognition of "first-line" chemotherapy and monoclonal agents for these conditions has given more urgency to the need to re-administer these drugs in cases of drug hypersensitivity reactions. Therefore, in these cases, not only is desensitization considered when there is no alternative therapy available but also when alternative treatments are considered therapeutically inferior and/or more toxic. In this article, we describe the steps involved in the evaluation of these patients, factors to consider before making a decision to desensitize, the implementation of desensitization protocols, and the outcomes of such procedures. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:13-9)**

Key words: *Allergy; Drug challenge; Drug desensitization; Skin testing; Monoclonal antibody; Chemotherapeutic agent; Adult; Pediatric; Hypersensitivity reactions*

The incidence of hypersensitivity reactions (HSR) to chemotherapeutic agents has increased as more cancer survivors are exposed to repeated courses of sensitizing agents.[1] In general, such reactions are especially common when platinum compounds, taxanes, epipodophyllotoxins, procarbazine, and L-asparaginase are administered.[2] In addition, treatment with murine and humanized mAbs have been reported to cause cutaneous and systemic allergic reactions in children and adults. The clinical significance of these reactions has increased due to the efficacy of these drugs in treating various malignancies and chronic inflammatory conditions as well as other diseases. Patients who develop HSRs to a medication in most cases may switch to an alternative drug, but coming to such a decision is more complicated when the offending medication is essential or the best treatment option.

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Abbreviations used
HSR- Hypersensitivity reaction
mAb- Monoclonal antibody

This is particularly true for cancer and debilitating chronic inflammatory conditions for which effective drugs may be limited. Therefore, drug desensitization is more likely to be needed in these cases.

INDICATIONS AND EVALUATION

The decision to desensitize should not be taken lightly given the resources needed and the possibility of breakthrough reactions. There should be compelling reasons, such as the lack of a viable alternative medication, before desensitization is considered. Other potential indications include the alternative medication having less efficacy and/or greater potential for toxicity. An algorithm that describes factors to be evaluated and considered before making a decision to desensitize a patient is outlined in Figure 1.

HISTORY

A detailed history is of utmost importance and should specify the clinical features of the reaction. Rapid drug desensitization protocols induce a temporary state of tolerance to a drug that has caused an immediate onset HSR. Because the putative target cells of desensitization are mast cells and possibly basophils, reactions amenable to desensitization usually are acute onset, and occur during or immediately after the infusion (<1 hour). The symptoms and/or signs include pruritus, flushing, urticaria, angioedema, dyspnea, chest tightness, wheezing, lightheadedness and/or dizziness, tachycardia, hypotension, syncope, nausea, abdominal cramps, and vomiting and/or diarrhea. Severe back or chest pain and a vague sense of impending doom have also been described by patients who experience acute anaphylactic reactions, especially to taxanes.

Non-mast-cell-mediated inflammatory reactions are typically not amenable to treatment by desensitization. Examples of such conditions include serum sickness, hemolytic anemias, thrombocytopenia, drug-induced interstitial nephritis, pneumonitis, hepatitis, vasculitis, and blood cell dyscrasias.[3] It also is important to recognize that some reactions may represent a direct adverse effect of the medication itself. An example of an adverse reaction that may mimic a HSR is liposomal doxorubicin, which is known to sometimes cause palmoplantar erythrodysesthesia ("hand-foot syndrome"), stomatitis, and/or a diffuse follicular eruption with an intertriginous distribution.[4-6] Absolute contraindications for desensitization include the following: Stevens-Johnson syndrome, bullous dermatitis, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms syndrome, and acute generalized exanthematous pustulosis (acute generalized exanthematous pustulosis).[3,7]

SKIN TESTING AND LABORATORY EVALUATION

If possible, skin testing to the offending medication should be done in the outpatient setting, preferably at least 2 weeks after a reaction has occurred, to ensure that skin test sensitivity is not diminished due to mast cell depletion of vasoactive mediators in the wake of an anaphylactic reaction. Skin testing is perhaps most useful in evaluating patients with reactions to platin-based drugs, which are known to induce IgE-mediated reactions. Skin prick and intradermal testing to platin-based drugs has a high negative predictive value, of 92%-99%, which makes this procedure useful in identifying those patients who could likely continue receiving their chemotherapy without desensitization.[8] However, there is not yet a standard approach for skin testing to these drugs and different concentrations have been used in the protocols that have been reported.[8-10] If the clinical suspicion is high despite a negative skin test, then a graded challenge protocol (discussed below) could be used to determine if the patient could safely return to regular infusion visits in the future.

Skin testing to other chemotherapeutic agents may not be possible due to cutaneous toxicity (ie, liposomal doxorubicin) or not well validated because the sensitivity and specificity of skin testing is unknown. In addition, a variety of monoclonal agents and paclitaxel can cause acute infusion reactions with the first or second exposure. These most likely represents non-IgE mediated systemic reactions versus pre-existing sensitization to an unspecified cross-reactive hapten or antigen. Although Brennan et al[11] published limited skin test data on a small number of patients tested by using prick and intradermal concentrations against infliximab (6 patients), trastuzumab (2 patients), and rituximab (9 patients), a more recent article, by Matucci et al,[12] describes a study that examined the results of skin testing of 23 patients with infliximab allergy. Only 7 of 23 patients (30.4%) had a positive skin test, but those patients were more likely to have experienced a severe reaction defined as grade 3 anaphylaxis by the Brown criteria (5/7 patients with a positive skin test).[13] Although the conclusions of Matucci et al. may or may not extend to other monoclonals, their study illustrates how skin test data can potentially be a useful instrument in risk-stratifying patients for desensitization even when the overall sensitivity is suspect.

In addition, some *in vitro* tests may be helpful in the evaluation of these patients. An elevated serum tryptase level (>11 ng/mL) drawn at the time of the reaction can be especially informative. If elevated, a baseline tryptase also should be drawn to screen for mastocytosis as a contributory factor in the patient's reaction. Other, more general, potentially helpful laboratory data include a complete blood cell count with differential, erythrocyte sedimentation rate, complement levels, and liver function tests.[7] There currently are no US Food and Drug Administration approved IgE tests for chemotherapy or monoclonal allergy although various groups have developed their own IgE-based assays for research purposes.

GRADED CHALLENGE

If the history and the results of available diagnostic testing are inconclusive for making a diagnosis of a drug-induced immediate HSR, then graded challenge to the drug can be performed as long as there is no history of anaphylaxis or other severe reactions. Drug challenge differs from desensitization in which the patient is assumed to be allergic to the medication in question. Drug challenge does not attempt to induce tolerance but is merely performed to observe if giving a small test dose of a drug (typically approximately 10% of the full dose) can provoke a reaction, albeit mild and easier to intervene upon than if a full dose were given.[14,15] The absence of hypersensitivity symptoms and/or signs with graded challenge essentially rules out immediate HSR to the medication in question. Drug challenge is thus a diagnostic tool unlike desensitization, which is intended as a

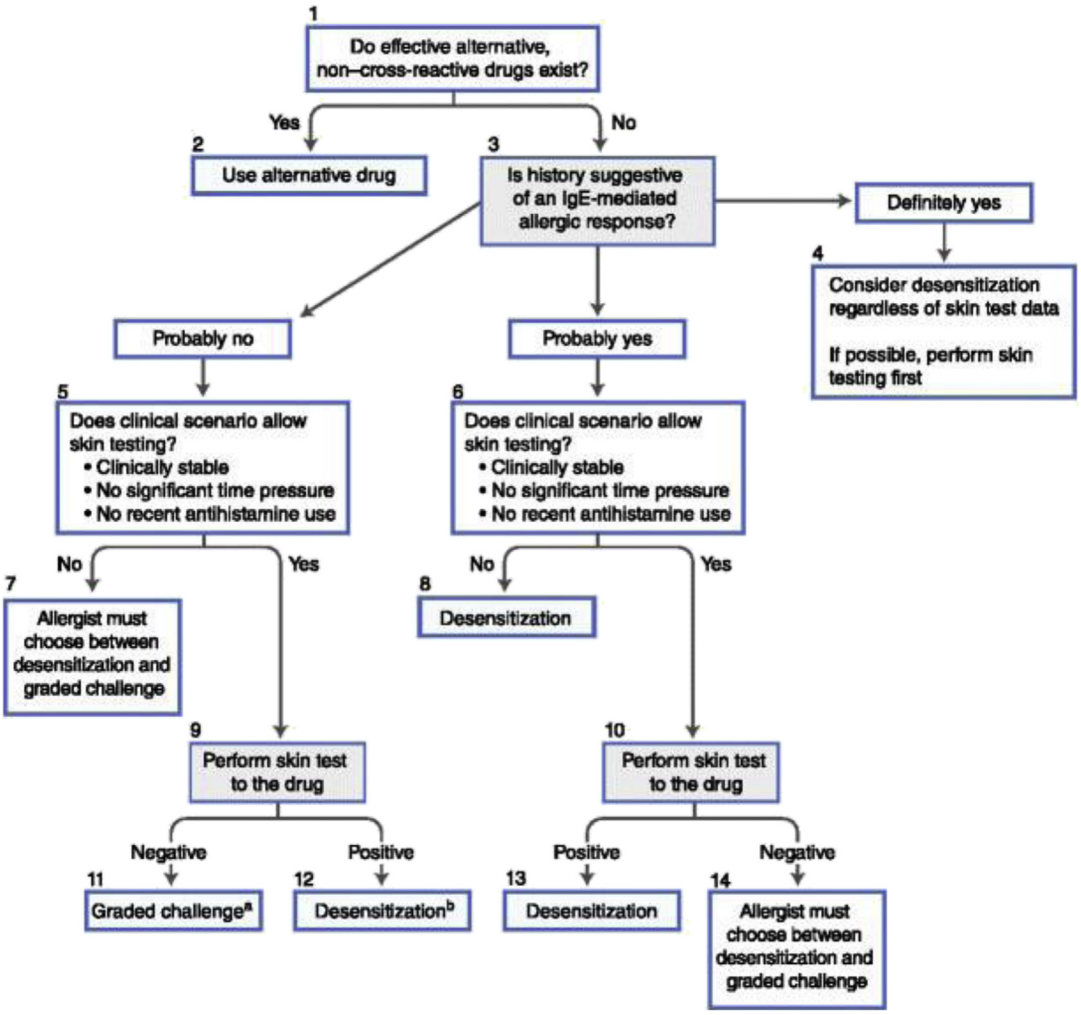

FIGURE 1. Stepwise approach to evaluation and treatment of patients with drug allergy. This approach cannot be used in cases of some severe reactions including Steven-Johnson syndrome; toxic epidermal necrolysis; drug reaction with eosinophilia and systemic symptoms syndrome; and drug-induced nephritis, hepatitis, or hemolysis. Reprinted with permission.[7]

therapeutic tool. Various challenge protocols exist at different institutions, but the general principle involves giving a small fraction of the total prescribed dose under carefully monitored conditions and proceeding to administer the remainder of the drug only if the challenge dose is tolerated. The Brigham and Women's Hospital graded challenge protocol involves giving approximately 1/10th the final intended dose over 3 rapid intervals followed by administering the rest of the dose at an infusion rate of 80 mL/h. If the graded challenge is tolerated, then the patient may return to regular infusion. Otherwise, a reaction (pruritus, flushing, urticaria, angioedema, dyspnea, chest tightness, wheezing, lightheadedness and/or dizziness, tachycardia, hypotension, syncope, nausea, abdominal cramps, vomiting and/or diarrhea) during graded challenge indicates that desensitization should be undertaken if the drug were to be administered again. In the pediatric population, a more cautious approach may be considered given the relative lack of ability to convey the onset of subjective symptoms, particularly in younger children (ie, itching, nausea, shortness of breath, and/or throat and/or chest tightness) when they occur. The graded challenge protocol used at Boston Children's Hospital starts at 1/100th of the therapeutic dose followed by 1/10th of the therapeutic dose and finally 9/10th of the therapeutic dose given at 30-minute intervals administered at the usual recommended infusion rate of the drug. The patient is then observed for 1 hour after the final dose. Given the possibility of a reaction that occurs during graded challenge to chemotherapy and monoclonal drugs, these procedures should be done under close monitoring with one-to-one nursing and rescue medications (antihistamines, epinephrine, corticosteroids, oxygen, albuterol) readily available.

PROTOCOLS

Grading, location, and informed consent

Once the decision to desensitize is made, categorizing a patient's anaphylaxis severity can be helpful in determining the appropriate setting for desensitization. A useful anaphylaxis grading system was described by Brown[13] who subdivided anaphylaxis into grade 1 through 3 reactions defined primarily by kind and degree of organ system involvement. Grade 1 reactions are strictly cutaneous

reactions, whereas grade 2 reactions include symptoms that implicate respiratory, cardiovascular, or gastrointestinal involvement (ie, stridor, lightheadedness, or sudden nausea/vomiting or diarrhea). Severe grade 3 reactions are defined by symptoms connected with altered vital signs (ie, hypoxia, hypotension, syncope).

Some centers require all desensitizations to be performed in the intensive care unit due to the need for vigilant monitoring with one-to-one nursing. Yet the data from Castells et al[10] demonstrate that the vast majority of patients undergoing desensitization have no reactions or mild cutaneous reactions, easily treated with pausing the infusion and treating with antihistamines.[16] Therefore, given the favorable outcome data in adults, it may be appropriate to reserve the intensive care unit only for patients at high risk who have had severe grade 3 anaphylaxis by the Brown criteria or those with minimal cardiopulmonary reserve capacity. Other adult patients may be desensitized in an outpatient infusion setting with appropriate one-to-one nursing and supervision by a specialist trained in recognizing and treating anaphylaxis. This is currently the practice at Brigham and Women's Hospital/Dana Farber Cancer Institute for adult patients. In children, given the lack of availability of large-scale studies as well as the fact that subjective symptoms are less likely to be communicated, more cautious observation is recommended. At Boston Children's Hospital, pediatric patients with grade 1 or 2 reactions undergo desensitization in the intensive care unit step-down unit whereas those with grade 3 reactions are desensitized in the intensive care unit. Informed consent must be obtained before every desensitization, and the potential risks, benefits, and alternatives of such process must be reviewed with the patient and/or the patient's parents.

Pretreatment

Pretreatment regimens vary from center to center and are aimed at preventing or minimizing the severity of any breakthrough reactions. They frequently include diphenhydramine (25 mg orally or intravenously for adults and 1 mg/kg for children), famotidine (20 mg intravenously for adults and children 12 years of age and older) and/or ranitidine (50 mg intravenously for adults and 1.5 mg/kg for children), administered 20 minutes before the initiation of the protocol. Because most reactions tend to occur toward the end of most desensitization protocols, it may be more advantageous to premedicate with second- and third-generation antihistamines with longer half-lives over shorter-acting first-generation antihistamines. This is the current practice at Brigham and Women's Hospital/Dana Farber Cancer Institute, and is also practiced at Boston Childrens Hospital (unpublished data). Some centers also administer antiemetic doses of dexamethasone (20 mg orally or intravenously for adults and 10 mg/m^2 for children, maximum 20 mg) given the previous night and the morning of desensitization for certain chemotherapeutic agents.[1] Additional pretreatment with montelukast (10 mg orally for adults and children >14 years old; 5 mg for children 6-14 years; 4 mg for children 2-5 years old) and/or acetylsalicylic acid at the oral dose of 325 mg for adults and 10-15 mg/kg per dose in children 1 hour before desensitization may be considered, particularly in patients who have previously failed desensitization or for those who have experienced flushing reactions.[17] Premedication with acetaminophen (500 mg for adults and 15 mg/kg for children) plus histamine blockers is recommended as prophylaxis for cytokine release reactions induced by mAbs used in cancer therapy.[18]

Desensitization protocols

Although desensitization protocols for chemotherapeutic agents vary from group to group, they all involve giving the offending medication at very low doses (1×10^{-2} to 1×10^{-3} dilutions) initially and gradually increasing until the complete prescribed dose is administered. Early attempts at readministering carboplatin or paclitaxel to patients with a history of previous HSRs date back to the 1990s, beginning with slow infusion protocols combined with antihistamine and steroid premedication.[19] When this did not succeed, other attempts at desensitization usually involved premedication with steroids and antihistamines followed by serial administration of 10-fold dilutions of the full-strength chemotherapy dose (typically starting at 1×10^{-3} dilution) as tolerated until the patient was able to receive the entire dose in full-strength concentration. Starting in the early 2000s, it was recognized that patients could tolerate more-rapid protocols, on the order of 4-6 hours, so long as starting doses were very small and the patients received routine premedication with antihistamines and steroids.[20] Lee et al[16] demonstrated the efficacy of a more rapid multisolution and multistep desensitization protocol in 2004 administered over approximately 6 hours and preceded with antihistamine premedication and no steroids. Ten patients who had previously experienced acute infusion reactions to carboplatin were desensitized; 4 of these patients had a skin test positive to carboplatin. Among 35 desensitizations, 31 were reaction-free (89%). Two patients had mild cutaneous reactions, 1 patient had anxiety and/or tachycardia, and 1 patient experienced dyspnea and desaturation. This initial study was followed up with a larger series of 98 patients with various malignancies (ovarian and breast being the most common) who received a total of 413 desensitizations to carboplatin and other chemotherapeutic agents, including cisplatin, oxaliplatin, paclitaxel (intraperitoneal and intravenous routes), doxorubicin, and rituximab.[10] Selected patients had either a history strongly consistent with an acute HSR and/or a positive skin test. All patients received a 3-solution, 12-step protocol, shown in the Figure 2, which demonstrated the wide applicability of the protocol to different medications. In addition, this protocol is adaptable to various contingencies and more accurate documentation of timing of reactions because vital signs and other clinical observations are noted with each step of the protocol. This information is useful for subsequent desensitizations because a patient with a history of breakthrough reactions may receive additional antihistamine treatment before the step at which previously experienced reactions occurred. Similar protocols have been used at Boston Children's Hospital in the pediatric population (unpublished data). In a recent review by Ruggiero et al,[2] the experience with other protocols for the pediatric populations has been summarized for a variety of chemotherapeutic agents, including carboplatin, L-asparaginase, methotrexate, taxanes, etoposide, VP16, procarbazine, anthracyclines, and cyclophosphamide. The type of HSRs amenable to these desensitizations were mainly reported as type I, IgE-mediated based on clinical history, and validated skin testing results for platin salts. However, skin testing to L-asparaginase and high-dose methotrexate showed high rates of false-negative results.

Various protocols, including that of Castells et al,[10] have been successfully applied to a variety of monoclonal agents, including infliximab and trastuzumab in addition to rituximab.[21] A similar rapid desensitization protocol was reported in the single pediatric case report of desensitization to rituximab.[22] In addition, this

Name of medication: ***Carboplatin***

Target Dose (mg)	250.0
Standard volume per bag (ml)	250
Final rate of infusion (ml/hr)	80
Calculated final concentration (mg/ml)	1
Standard time of infusion (minutes)	187.5

					Total mg per bag
Solution 1	250	ml of	0.010	mg/ml	2.500
Solution 2	250	ml of	0.100	mg/ml	25.000
Solution 3	250	ml of	0.992	mg/ml	248.033

*** PLEASE NOTE *** The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are *not completely infused*

Step	Solution	Rate (ml/hr)	Time (min)	Volume infused per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0050	0.0050
2	1	5.0	15	1.25	0.0125	0.0175
3	1	10.0	15	2.50	0.0250	0.0425
4	1	20.0	15	5.00	0.0500	0.0925
5	2	5.0	15	1.25	0.1250	0.2175
6	2	10.0	15	2.50	0.2500	0.4675
7	2	20.0	15	5.00	0.5000	0.9675
8	2	40.0	15	10.00	1.0000	1.9675
9	3	10.0	15	2.50	2.4803	4.4478
10	3	20.0	15	5.00	4.9607	9.4085
11	3	40.0	15	10.00	9.9213	19.3298
12	3	80.0	174.375	232.50	230.6702	250.0000

	Total time (minutes) =		339.375	= 5.66 hrs		

FIGURE 2. Example of 3-solution, 12-step desensitization protocol.[10]

protocol has been successfully used for desensitization in pediatric patients with HSRs to mAbs at Boston Children's Hospital (unpublished data). Puchner et al[23] reported successful desensitization to infliximab of 1 pediatric patient by using a different protocol, which included 11-step escalating increments, with 15-minute intervals administered over a period of 6 hours.

Treatment of reactions during desensitization

The treatment of breakthrough reactions, when they occur, varies from center to center. In the large case series of 413 desensitizations described by Castells et al,[10] most reactions were mild cutaneous reactions that did not result in aborted treatment. The risk of serious anaphylaxis remains, however; so, having necessary intervention medications such as epinephrine, antihistamines, bronchodilators, and steroids at the bedside is essential. Even more imperative is the need for trained staff who supervise the desensitization at all times because early recognition of anaphylaxis leads to better treatment outcomes.[24] Mild cutaneous reactions such as pruritus, flushing, and/or isolated hives can be treated with intravenous administration of an H1 blocker such as diphenhydramine (25-50 mg for adults, 1 mg/kg for children; a maximum single dose of 50 mg) with or without an H2 blocker such as intravenous ranitidine (50 mg for adults, 1.5 mg/kg for children; a maximum single dose of 50 mg). Patients who experience respiratory symptoms such as chest tightness or shortness of breath should receive a bronchodilator in addition to antihistamines and supplemental oxygen if needed. For more-severe reactions, intravenous methylprednisolone (0.5 mg/kg) can be given, and, for severe life-threatening anaphylactic reactions that feature status asthmaticus, syncope, and/or airway loss from angioedema, intramuscular epinephrine (0.3 mg for adults, 0.01 mg/kg for children; a maximum single dose of 0.3 mg) should be immediately administered. As soon as a reaction is noted, the infusion is stopped, and once the reaction has resolved, the infusion is restarted at the point of interruption. Slowing the infusion rate and/or adding additional steps to the protocol may also be considered.[11] For patients who continue to react despite these measures, additional pretreatment with montelukast and acetylsalicylic acid as mentioned earlier may be effective as well.[17]

OUTCOMES

In the largest case series of rapid desensitizations to chemotherapeutic agents reported by Castells et al,[10] 67% proceeded without HSR, 27% had only mild reactions (classified as absence of chest pain, changes in blood pressure, dyspnea, oxygen desaturation, or throat tightness) and 6% were characterized by severe HSRs. However there were no intubations or deaths. Only one desensitization required epinephrine administration, and all patients in the case series were able to receive their full target dose. For patients who received multiple desensitizations, most reactions occurred during the first 5 desensitization (94.8%), with the majority of the reactions occurring during the first 2 desensitizations (61%). All reactions subsided when the infusion was stopped and appropriate treatment was administered. Epinephrine was only used in one case, no patient required transfer to a more acute care setting or intubation, no deaths occurred, and all the patients received their full target dose.[10] Carboplatin desensitization by using a modified desensitization protocol was reported as successful by Lazzareschi et al[25] in 6 children; however, Lafay-Cousin et al[26] report a much lower success rate, of approximately 50%. There have been a number of successful desensitizations to other chemotherapeutic agents in the pediatric population even though these are mostly limited to case reports.[2,27]

A follow-up study by Brennan et al[11] that focused on monoclonal agents also showed a high success rate, with 104 of 105 desensitizations successfully completed. They observed HSRs during 29% of desensitizations, including 27 mild reactions, 1 moderate reaction, and 2 severe reactions. Overall reactions during desensitization were markedly less severe than in initial HSRs. The experience with desensitization to mAbs in pediatrics has been promising but is again limited to case reports.[22,23] In addition, there have been a number of successful desensitizations to chemotherapeutic agents as well as mAbs at Boston Children's Hospital (unpublished data).

CONCLUSIONS

Drug desensitization to chemotherapeutic agents and mAbs is a highly effective readministration strategy for those patients who develop HSRs to their needed medications, given their limited therapeutic options. The immunologic basis of all chemotherapy-induced HSRs and successful desensitization outcomes cannot always be quantitatively assayed because validated skin test reagents and protocols may not exist for every drug. Nevertheless, desensitization protocols use gradual dose escalation to allow for safe treatment with a medication to which a patient has previously had a systemic reaction, thus achieving the desired clinical outcome. The process requires special training and coordination of a team of allergy care providers, nurses, pharmacists, and hospital administrators who work together to safely and successfully implement desensitization protocols when appropriate. Although the work described in this review demonstrates the efficacy of preventing the recurrence of previous mild and severe HSRs through desensitization, further clinical research is needed to show whether the technique has an impact on other care metrics such as survival and length of time to disease progression.

Although the molecular and cellular mechanism(s) of drug desensitization have yet to be clearly elucidated, most research has focused on the role of mast cells and basophils that express the IgE receptor. Possible nonexclusive mechanisms include the downregulation of the IgE receptor, downregulation of signaling molecules downstream of the IgE receptor such as Syk kinase, or upregulation of inhibitory signaling molecules such as SH2 domain-containing inositol 5'-phosphatase (SHIP).[28,29] Impaired signaling downstream of FceRI secondary to desensitization *in vitro* results in attenuation of early and late onset activation events, including degranulation and inflammatory cytokine release (TNF-a and IL-6).[30] Although understanding the basic mechanisms of desensitization is beyond the scope of this review, mast cells and possibly basophils are involved as proven by the observation that patients who undergo desensitization to carboplatin temporarily lose their skin test reactivity.[19,31] Further bench and translational work will lead to a better understanding of the cellular and molecular mechanisms behind drug desensitization. These findings, it is hoped, will lead to the development of new diagnostic and therapeutic tools to further improve patient care and outcomes in this arena.

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